REMARKS

Status of the Claims

Claims 1-3, 5-8, 22-24, 26-29, 32-37 and 50-73 are in the application.

Claims 1-3, 5-8, 22-24, 26-29, 32-37 and 50-73 are rejected.

Upon entry of this response, claims 1-3, 5-8, 22-24, 26-29, 32-37 and 50-73 will be pending and subject to examination.

Rejections under 35 U.S.C. § 103

Claims 1-3, 5-7, 22-24, and 26-29 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Chen *et al.* (WO 98/53843) in view of Wang *et al.* (WO 99/67293) in view of Hollis *et al.* (U.S. Patent No. 5,629,415) and in view of Rutter (U.S. Patent No. 4,769,326). The Office alleges that the Chen reference discloses vaccine constructs comprising the membrane bound domain of IgE coupled to heterologous sequences including helper T epitopes. The Office acknowledges that the Chen reference fails to disclose a composition with a proteolytic cleavage sequence. The Office alleges the deficiency is remedied by the Rutter reference which allegedly discloses the use of linkers comprising proteolytic cleavage sites because the linkers "allow for efficient incorporation and removal of desired functional properties." (Final Office Action p. 5). Applicants respectfully disagree.

Claims 1-3, 5-7, 22-24, and 26-29 are not obvious because the Office has failed present a proper *prima facie* obviousness rejection because the cited references teach away from the claimed invention. The Chen and Wang references teach away from using a proteolytic cleavage sequence, which would allow the components of the construct to be unconjugated. One of skill in the art reading the Chen and Wang references would be led to use a composition that conjugates the two components without the two components being able to be cleaved. For example, the Chen reference repeatedly describes conjugates and does not state that the conjugated composition can include a cleavage sequence. Additionally, the Chen reference states that for conjugates in human use one would expect that there would be "no inhibition of IgE responses to unrelated, ***unconjugated*** antigens." (Chen, p. 10, line 22, emphasis added.). "'A reference may be said to teach away when a person of ordinary skill, upon reading the

reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant.'" *Optivus Tech., Inc. v. Ion Beam Applications S.A.*, 469 F.3d 978, 989 (Fed. Cir. 2006) (quoting *In re Kahn*, 441 F.3d 977, 990 (Fed. Cir. 2006)). Here, the Chen reference teaches away because it states that there would be no inhibition of IgE responses for unconjugated antigens. Therefore, one of skill in the art reading the Chen reference in its entirety would not have inserted a proteolytic cleavage sequence because such a construct would lead to an unconjugated composition leading to a result that is not desired. Accordingly, the Chen reference teaches away from using a construct that would allow the epitopes to be separated by use of a cleavage sequence.

The Wang reference also teaches away from including a proteolytic cleavage sequence. The Wang reference discloses the use of a spacer between its components and states that the two components are "adjacent to either the N- or C-terminus of IgE-CH3 domain antigen sequences, ***in order to evoke efficient*** antibody responses." (Wang, p. 28-29). Like the Chen reference, the Wang reference teaches that the components should be next to one another and linked so that there is a proper response. The Wang reference fails to suggest decoupling the components and teaches away from such a method because it would not "evoke [an] efficient antibody response[]."

Accordingly, one of skill in the art would not have used a proteolytic cleavage sequence because the Wang and Chen references teach away from allowing the components to be separated. In view of the foregoing, Applicants respectfully request that the rejection under 35 U.S.C. § 103(a) be withdrawn.

Claims 1-3, 5-7, 22-24, and 26-29 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Klysner *et al.* (WO 02/20038) in view of Wang *et al.* (WO 99/67293) and in view of Rutter. Claims 1-3, 5-7, 22-24, and 26-29 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Klysner *et al.* (US 2002/0172673) in view of Wang *et al.* (WO 99/67293) and in view of Rutter. The Office acknowledges that the Klysner reference fails to disclose the use of linkers comprising a proteolytic cleavage sequence between the epitopes.

(Office Action, page 6). The Office alleges that the Rutter reference cures this deficiency. Applicants respectfully disagree.

The claims are not obvious because the Klysner and Wang references each teach away from inserting a proteolytic cleavage sequence. The Wang reference teaches away for the reasons stated above. The Klysner reference also teaches away because the Klysner reference teaches that the epitopes described in Klysner should be simultaneously presented by the antigen presenting cells. (Klysner, p. 13, lines 14-20)[1]. The inclusion of a proteolytic cleavage sequence that allows the epitopes to be separated would function to reduce the likelihood of simultaneous presentation of the epitopes by the antigen presenting cells. One of skill in the art would not have been led to insert a proteolytic cleavage sequence because it would be contrary to what the Klysner reference states is necessary for an effective use, that is the simultaneous presentation of the epitopes by the antigen presenting cells. Thus, the Klysner reference teaches away from using a proteolytic cleavage sequence.

Accordingly, the Office has failed to make a proper *prima facie* obviousness rejection because the combination of the references teaches away from the claimed invention.

Therefore, the claims are not obvious because the Klysner and Wang references teach away and because the combination of the references would not have suggested one of skill in the art to insert a proteolytic cleavage sequence. In view of the foregoing, Applicants respectfully request that the rejection under 35 U.S.C. § 103(a) be withdrawn.

Claims 8, 32-37, 50, 58-73 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Chen et al (WO 98/53843) in view of Wang et al. (WO 96/67293) in view of Hollis et al. (U.S. Patent No. 5,629,415) and in view of Rutter (U.S. Patent 4,769,326) as applied to claims 1-3, 5-7, 22-24, and 26-29, and further in view of Walls et al. (Nucleic Acids Research, 1993, 21:2921-2929) as evidenced by Janeway et al (Immunobiology, 3rd Edition, Garland Publications, 1997, pages 3:26-3:31). Claims 8, 32-37, 50, 58-73 stand rejected under

[1] Applicants note that the two Klysner references are the same. Page and line number refer to WO 02/20038

35 U.S.C. § 103(a) as allegedly being unpatentable over Klysner (WO 02/20038) in view of Wang et al. (WO 96/67293) in view of Hollis et al. (U.S. Patent No. 5,629,415) and in view of Rutter (U.S. Patent 4,769,326) as applied to claims 1-3, 5-7, 22-24, and 26-29, and further in view of Walls et al. (Nucleic Acids Research, 1993, 21:2921-2929) as evidenced by Janeway et al (Immunobiology, 3rd Edition, Garland Publications, 1997, pages 3:26-3:31). Claims 8, 32-37, 50, 58-73 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Klysner (US 2002/0172673) in view of Wang et al. (WO 96/67293) in view of Hollis et al. (U.S. Patent No. 5,629,415) and in view of Rutter (U.S. Patent 4,769,326) as applied to claims 1-3, 5-7, 22-24, and 26-29, and further in view of Walls et al. (Nucleic Acids Research, 1993, 21:2921-2929) as evidenced by Janeway et al (Immunobiology, 3rd Edition, Garland Publications, 1997, pages 3:26-3:31). Applicants respectfully disagree because the combination fails to yield the claimed invention.

The Office alleges that the combination of references discloses each and every element of claims 8, 32-37, 50, 58-73. In support of this contention the Office states:

> Note that as evidenced by Janeway et al., immunoglobulin genes are assembled via the process of V(D)J recombination, and that different isotypes (i.e. IgG, IgE, IgA) are obtained by isotype switching. As such the immunoglobulin heavy chain leader sequence is upstream of the rearranged variable domain . . . and thus an "IgE leader" is the ***same sequence*** as an IgM, IgD, IgG, and IgA leader sequence…Thus, the "Ig leader" of Walls *et al.* is an "IgE leader."

(Office Action, pages 9-10, emphasis added). Applicants enclose herewith a declaration pursuant to 37 C.F.R. § 1.132 by Dr. David B. Weiner. The declaration lists the amino acid sequences from IgE variable, IgA constant, IgA, variable1, IgA variable 2, IgA variable 3, IgG constant, IgM variable, and IgM VH1. The declaration also shows the sequence similarity between the different leader sequences. The IgE leader sequence is not 100% identical to the other leader sequences. The declaration states, "[t]he alignments show that IgE leader sequence is not the same as the leader sequences from the different isotypes." (Declaration, ¶ 3). Therefore, the "Ig leader" of the Walls reference is not an "IgE leader." Therefore, the Office has failed to present a proper *prima facie* obviousness rejection because even if all the references

were combined the combination does not yield the present invention. Thus, the claims are not obvious.

In view of the foregoing, Applicants respectfully request that the rejection under 35 U.S.C. § 103(a) be withdrawn.

Conclusion

Claims 1-3, 5-8, 22-24, 26-29, 32-37 and 50-73 are in condition for allowance. A notice of allowance is earnestly solicited. Applicants invite the Examiner to contact the undersigned at 610.640.7820 to clarify any unresolved issues raised by this response.

The Commissioner is hereby authorized to charge any deficiencies of fees and credit of any overpayments to Deposit Account No. 50-0436.

Respectfully submitted,

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Enclosures: Declaration of David B. Weiner pursuant to 37 C.F.R. § 1.132.